ACUTE TOXICITY SUMMARY

AMMONIA

(anhydrous ammonia, aqueous ammonia)

CAS Registry Number: 7664-41-7

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**3,200 µg/m³**
Critical effect(s)	eye and respiratory irritation
Hazard Index target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless gas
Molecular formula	NH_3
Molecular weight	17.03
Density	0.695 g/L @ 25°C
Boiling point	-33.5°C
Melting point	-77.7°C
Vapor pressure	6,460 mm Hg @
Flashpoint	unknown
Explosive limits	unknown
Solubility	very soluble in water, alcohol and ether
Odor threshold	17 ppm (geometric mean) (AIHA, 1989)
Odor description	sharp and very irritating
Metabolites	unknown
Conversion factor	1 ppm = 0.71 mg/m³ @ 25°C

III. Major Uses or Sources

Ammonia is a strongly alkaline chemical which is widely used in industry as a feed stock for nitrogen based chemicals such as fertilizers, plastics and explosives (ATSDR, 1990). Nationwide, ammonia is the third most common chemical to be released accidentally (U.S.EPA, 1989). Among hazardous material incidents such as intentional and threatened releases, those involving ammonia are the sixth most common. The volatility of ammonia, along with its common method of storage as large quantities under pressure, results in a potential for release of large amounts of ammonia gas (NRC, 1987).

IV. Acute Toxicity to Humans

Ammonia vapors cause irritation of the eyes and respiratory tract. Higher concentrations cause conjunctivitis, laryngitis, and pulmonary edema, possibly accompanied by a feeling of suffocation (OSHA, 1989). Contact with the skin causes burns and blistering. The eye is especially sensitive to alkali burns. Ammonia combines with moisture in the eyes and mucous membranes to form ammonium hydroxide. Ammonium hydroxide causes saponification and liquefaction of the exposed, moist epithelial surfaces of the eye and can easily penetrate the cornea and damage the iris and the lens (CCOHS, 1988; Way *et al*., 1992). Damage to the iris may eventually lead to cataracts (CCOHS, 1988). Inhalation exposure to ammonia may result in an increase in systemic arterial blood pressure (Zitnik *et al*., 1969). Exposure can also cause a decrease in minute ventilation volume (Cole *et al*., 1977). Ammonia gas is especially irritating to upper respiratory passages, which prompts exposed victims to attempt escape from the fumes as quickly as possible. MacEwen and Vernot (1972) described pulmonary edema as the most frequent cause of death in humans exposed to ammonia.

Silverman and coworkers (1949) exposed 7 volunteers to 500 ppm (355 mg/m^3) ammonia for 30 minutes using an oral-nasal mask. Symptoms due to ammonia inhalation varied widely among the 7 subjects. All seven subjects experienced upper respiratory irritation, which was graded as severe in 2 subjects. Only 2 subjects were able to continue nasal breathing throughout the 30 minute exposure. Reactions included irritation of the nose and throat, hypoesthesia of the exposed skin, and lacrimation. In two subjects, the nasopharyngeal irritation persisted for 24 hours after the exposure. One of the 7 subjects was only exposed to ammonia for 15 minutes rather than the full 30 minutes. The reason for this deviation in the exposure regimen was not given. In a previous experiment, brief exposure to 1,000 ppm reportedly resulted in immediate coughing in human subjects.

Ferguson and coworkers (1977) used six human subjects to demonstrate that a tolerance to ammonia exposure of 100 ppm (71 mg/m^3) can be developed with a two-to-three week inurement period during which volunteers were exposed to lesser concentrations. The results tended to support the belief that persons with no recent history of ammonia exposure are more sensitive to the irritating effects than those who are acclimated to the noxious gas.

Verberk (1977) exposed sixteen subjects, eight previously exposed and eight naive, for two hours to ammonia in concentrations of 50, 80, 110, and 140 ppm (36, 57, 78, 99 mg/m^3). The naive group could not tolerate 140 ppm for two hours and had several complaints during exposure to 110 ppm for 1 hour. None of the subjects in the study demonstrated a decrease in measured pulmonary function tests, including vital capacity, forced expiratory volume (1 second), and forced inspiratory volume (1 second), following ammonia exposure. The results showed a greater sensitivity to ammonia exposure for the naive group for responses of smell, eye irritation, cough, general discomfort, headache, and irritation of the chest. At the end of the initial 30 minutes of the 2-hour exposure period, nuisance level smell, eyes, nose, or throat irritation, or cough urge were reported by 7 of 16 (44%), 9 of 16 (56%), 12 of 16 (75%), or 15 of 16 (94%) individuals at concentrations of 50, 80, 110, or 140 ppm, respectively.

MacEwen *et al*. (1970) exposed groups of 5 and 6 human subjects to respective ammonia concentrations of 30 and 50 ppm (21 and 36 mg/m³). The volunteers subjectively rated irritation for the 10-minute exposures. No moderate or higher irritation was discerned by the group at the lower exposure level; however, 4 of the 6 subjects rated the 10 minute exposure at 50 ppm as causing moderate irritation.

The Industrial Bio-Test Laboratories (1973) evaluated ten human subjects for the irritation threshold of ammonia from exposures to ammonia gas at four different concentrations: 32, 50, 72, and 134 ppm (23, 36, 51, and 95 mg/m³). Irritation was taken to be any annoyance to the eyes, nose, mouth, throat, or chest which persisted throughout the 5-minute exposure period. At 72 ppm three subjects experienced eye irritation, two had nasal irritation, and three had throat irritation. At 134 ppm, five of the ten subjects experienced lacrimation and eye irritation, seven complained of nasal irritation, eight had throat irritation, and one experienced chest irritation. The authors only used 5-minute exposure durations; and it is possible that irritation symptoms could have developed with longer exposure durations at the lower exposures. The authors discounted the significance of nasal dryness reported at the two lowest levels.

Douglas and Coe (1987) determined a lachrymatory threshold of 55 ppm for ammonia following approximately 15 second exposures of volunteers via tight-fitting goggles. The threshold for bronchoconstriction, determined as a 20% increase in airway resistance, was slightly higher at 85 ppm following 10 breaths of ammonia via mouthpiece.

Estimates of odor thresholds for ammonia vary from 0.04-103 ppm (0.03-73 mg/m³) (Ferguson *et al*., 1977; Henderson and Haggard, 1943; Ruth, 1986). Near the odor threshold, persons exposed to ammonia can experience annoyance and believe the odor to be a nuisance. Exposure to ammonia may result in an exacerbation of preexisting asthma. Shim and Williams (1986) surveyed 60 patients with a history of asthma worsened by certain odors. Nearly 80% of these patients claimed to have an exacerbation of asthma following exposure to household cleaners containing ammonia.

Predisposing Conditions for Ammonia Toxicity

Medical: Persons with asthma and other respiratory ailments including underlying cardiopulmonary disease (Shim and Williams, 1986) and persons with no tolerance, developed from recent exposures to ammonia (Ferguson *et al*. 1977), may be more susceptible to the toxic effects of ammonia.

Chemical: Chronic high dose aspirin therapy and therapy with valproic acid elevate blood ammonia levels (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The pulmonary lesions observed following acute, potentially lethal, inhalation of ammonia are similar in man and experimental animals (Withers, 1986; Payne *et al*., 1990). Male rats and mice were determined to be more sensitive to the lethal effects of ammonia than the females of either species (Appelman *et al*., 1982; Stupfel *et al*., 1971).

Several animal lethality studies published dose-response data from which the MLE_{05} (maximum likelihood estimate corresponding to 5% lethality) and BC_{05} (benchmark dose at the 95% lower confidence interval of the MLE_{05}) could be determined (see Table 1).

Table 1. Animal Lethality Effective and Benchmark Dose Levels for Ammonia

Reference	Species	Time (min)	MLE_{05} (ppm)	BC_{05} (ppm)
MacEwen & Vernot (1972)	rat	60	5,999	4,908
MacEwen & Vernot (1972)	mouse	60	4,006	3,406
Kapeghian *et al*. (1982)	mouse	60	3,664	3,366
Appelman *et al*. (1982)	rat	(10)*	11,862	9,950
Appelman *et al*. (1982)	rat	(20)*	13,010	10,206
Appelman *et al*. (1982)	rat	(40)*	11,137	4,881
Silver and McGrath (1948)	mouse	(10)*	2,846	2,298

* *Exposure time was adjusted to 60 min using a modification of Haber's Law to facilitate comparisons of MLE_{05} and BC_{05} values. Exponent n = 2 was determined, based on Appelman et al. (1982) rat lethality data, by varying the term in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983).*

Appelman *et al*. (1982) observed signs of restlessness, wet noses and nasal discharge in rats immediately after the start of inhalation exposure to ammonia. Mouth breathing and dyspnea occurred soon after the start of exposure. Eye discharge began about 30 minutes into the exposure, and signs of eye irritation after 60 minutes of exposure. Dose versus exposure time varied from 7,000 ppm (4,970 mg/m^3) for 60 minutes to 26,850 ppm (19,064 mg/m^3) for 10 minutes.

VI. Reproductive or Developmental Toxicity

There are no confirmed studies which show conclusively that reproductive or developmental toxicity can be linked experimentally or epidemiologically to ammonia exposure (Reprotext, 1999).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 3,200 µg/m³

Study	Industrial Biotest Laboratories, 1973; MacEwen *et al*., 1970; Silverman *et al*., 1949; Verberk, 1977
Study population	humans
Exposure method	inhalation
Critical effects	eye and respiratory irritation
LOAEL	varied (see Section IV of text)
NOAEL	varied (see Section IV of text)
Exposure duration	varied (see Section IV of text)
Extrapolated 1 hour concentration	13.6 ppm (BC_{05})
LOAEL uncertainty factor	not needed in BC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Reference Exposure Level	4.5 ppm (3.2 mg/m³; 3,200 µg/m³)

The exposure concentrations from the 4 studies were adjusted to 1-hour durations using the formula C^n x T = K (Table 2). The value for the exponent n was empirically derived from the preceding data sets. The value of n (in the formula C^n x T = K) was sequentially varied for the log-normal probit relationship analysis. Using a chi-square analysis, a value of n = 4.6 was found to be the best fit.

The REL was calculated by a benchmark concentration (BC) approach using a log-normal probit analysis (Crump and Howe, 1983; Crump. 1984). The 95% lower confidence limit of the concentration expected to produce a response rate of 5% is defined as the BC_{05}. The maximum likelihood estimate for a 5% response was 20.1 ppm and the 95% LCL on this value (BC_{05}) for ammonia from this analysis was 13.6 ppm.

Response rate	MLE (ppm)	95% LCL (ppm)
1%	13.4	7.8
5%	20.1	13.6 (BC_{05})

An uncertainty factor (UF) of 3 was used to account for intraspecies variation in the human population. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Table 2. Ammonia, Human Irritation, 60 Minute Exposures (adjusted), ppm

Study Concentration	32	30	50	50	72	50	80	134	110	140	500
Exposure Time (min.)	5	10	5	10	5	120	120	5	60	60	30
60 min. adjusted Concentration	19	20	29	34	42	43	69	78	95	120	430
Response	0/10	0/5	0/10	4/6	3/10	7/16	9/16	8/10	12/16	15/16	7/7
Study	2	3	2	3	2	1	1	2	1	1	4

Table adapted from: (1) Verberk, 1977; (2) Industrial Biotest Laboratories, 1973; (3) MacEwen et al., 1970; (4) and Silverman et al., 1949. The two lowest concentrations were combined for the log-probit analysis since this improved the fit of the data.

Level Protective Against Severe Adverse Effects

Exposure to 140 ppm (99.4 mg/m³) ammonia was considered 'unbearable' resulting in termination of exposure by all of 8 non-expert student volunteers after 30 to 75 minutes (Verberk, 1977). These exposures were tolerated for the full 2-hour exposure period by all 8 expert volunteers who were familiar with irritant vapors. Based on these findings in which ammonia inhalation resulted in a subjective response of panic or the need in naive subjects to take shelter, a 2-hour NOAEL of 110 ppm and a 30-minute LOAEL of 140 ppm were noted. Short exposures to ammonia did not result in increased nasal resistance of atopic subjects when compared to nonatopic subjects (McLean *et al*., 1979). The non-expert group was considered to be more like the general public in their response. The final value to protect against severe adverse effects from ammonia exposure is thus 110 ppm (78 mg/m³).

Level Protective Against Life-threatening Effects

Kapeghian *et al*. (1982) determined a 1-hour LC_{50} of 4,230 ppm and a 1-hour no observed lethality level of 3,440 ppm in male mice. The MLE_{05} and BC_{05} were estimated as 3,664 and 3,366 ppm (Table 1), respectively. The report by Kapeghian *et al*. (1982) provides one of the most detailed exposure and monitoring methods used for ammonia among the various animal lethality reports reviewed. In addition, a sensitive experimental animal species was used for the experiments (MacEwen & Vernot, 1972). An uncertainty factor of 1 was applied to account for animal to human extrapolation since (1) the BC accounts for some degree of variation and (2) OEHHA's comparison of human irritation thresholds with concentrations lethal to mice suggests humans are not more susceptible than mice to ammonia toxicity. That is, in examining the Verberk (1977) study and comparing it to the mouse lethality study, additional uncertainty factors to the mouse study results in a concentration below the Verberk (1977) human study. A factor of 10 was applied to account for individual human variation. The cumulative uncertainty factor was

10. The resulting level for ammonia to protect against life-threatening effects is 340 ppm (240 mg/m^3).

VIII. References

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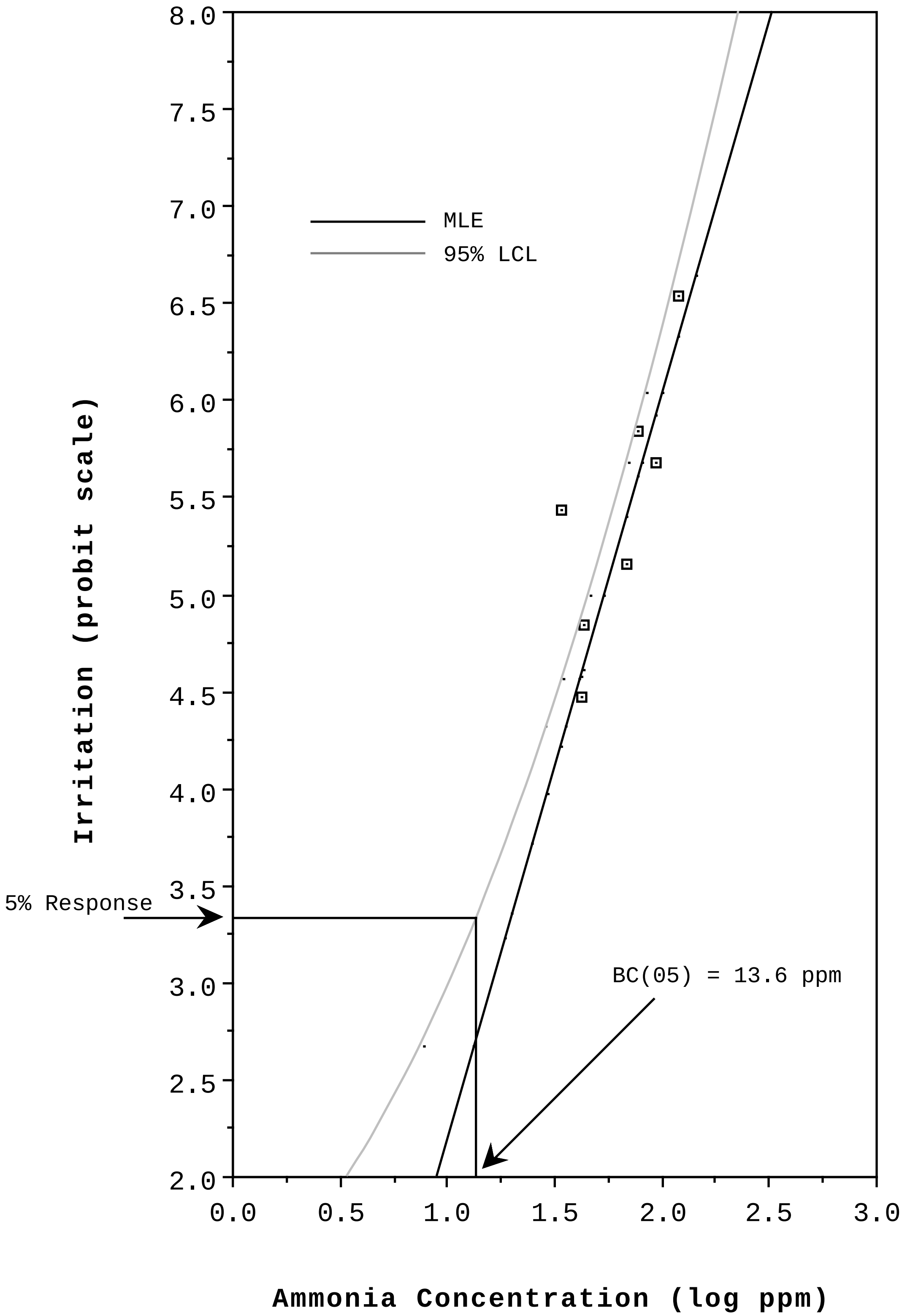
IX. Graphic Representation of Benchmark Concentration Determination



8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
MLE
95% LCL
Irritation (probit scale)
5% Response
BC(05) = 13.6 ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Ammonia Concentration (log ppm)